



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : A61K 31/57</p>	<p>A1</p>	<p>(11) International Publication Number: WO 95/03807 (43) International Publication Date: 9 February 1995 (09.02.95)</p>
<p>(21) International Application Number: PCT/AU94/00424 (22) International Filing Date: 27 July 1994 (27.07.94) (30) Priority Data: PM 0182 27 July 1993 (27.07.93) AU (71) Applicant (for all designated States except US): THE UNIVERSITY OF SYDNEY [AU/AU]; Sydney, NSW 2006 (AU). (72) Inventors; and (75) Inventors/Applicants (for US only): BILLSON, Francis, Alfred [AU/AU]; Dept. of Ophthalmology, The University of Sydney, Sydney, NSW 2006 (AU). PENFOLD, Philip, Leslie [AU/AU]; The University of Sydney, Dept. of Ophthalmology, Sydney, NSW 2006 (AU). (74) Agent: SPRUSON & FERGUSON; G.P.O. Box 3898, Sydney, NSW 2001 (AU).</p>		<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GR, HU, JP, KB, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published <i>With international search report.</i></p>
<p>(54) Title: TREATMENT OF AGE-RELATED MACULAR DEGENERATION</p> <div data-bbox="586 1150 1097 1392" data-label="Chemical-Block"> </div> <p>(57) Abstract</p> <p>The present invention relates to the treatment of inflammatory response in the macula of the eye by use of a depot injection into the vitreous humour of a suitable anti-inflammatory agent. In particular, this invention relates to the use of triamcinolone acetonide (I) which is in crystalline form and is sparingly soluble in the vitreous of the eye, and which does not leave any vision impairing residue in the eye, for the treatment of age-related macular degeneration.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Treatment of Age Related Macular Degeneration

Technical Field

The present invention relates to the treatment of inflammatory response in the macula of the eye^{1,2,3,4,5,6} by use of a depot injection into the vitreous humour of a suitable anti-inflammatory agent. In particular it relates to the treatment of age-related macular degeneration and more particularly relates to the treatment of the end stage of this condition with anti-inflammatory steroids. This end stage previously has been presumed to be untreatable.

Background Art

10 The major cause of registrable blindness in developed countries is due to the condition known as age-related macular degeneration⁷. In this condition, the macula which is a minute area in the centre of the retina is damaged. The macula occupies a total area of less than 1mm². This area is especially adapted for acute and detailed vision. In the central portion of the macula, known as the fovea (which is 0.4mm in diameter) the
15 blood vessels, and other cells are displaced to the side, allowing light to fall onto the photosensitive layer. This is in contrast to other parts of the retina where light has to pass through several layers of tissue before arriving at the photosensitive layer.

The condition itself is conveniently divided into three stages. It may present as early stage macular degeneration. At least 20% of patients develop an active
20 neurovascular form.

One end stage of this condition is known as atrophic macular degeneration (AMD) while a second end stage is known as neovascular macular degeneration (NMD), which is caused when new blood vessels begin to grow under the retina, particularly the macula.

AMD is not treatable, whereas NMD in some cases may be relieved by laser
25 treatment. However, a complication of laser treatment is actual loss of vision. In addition, laser treatment, where applicable, is not always a permanent cure since the blood vessels may begin to grow again.

The problem of macular degeneration is immense. It has been estimated that 25% of people 70 and over in the developed world will have the mild form of the condition
30 while 1 in 10 have severe symptoms and 1 in 100 progress to complete blindness.

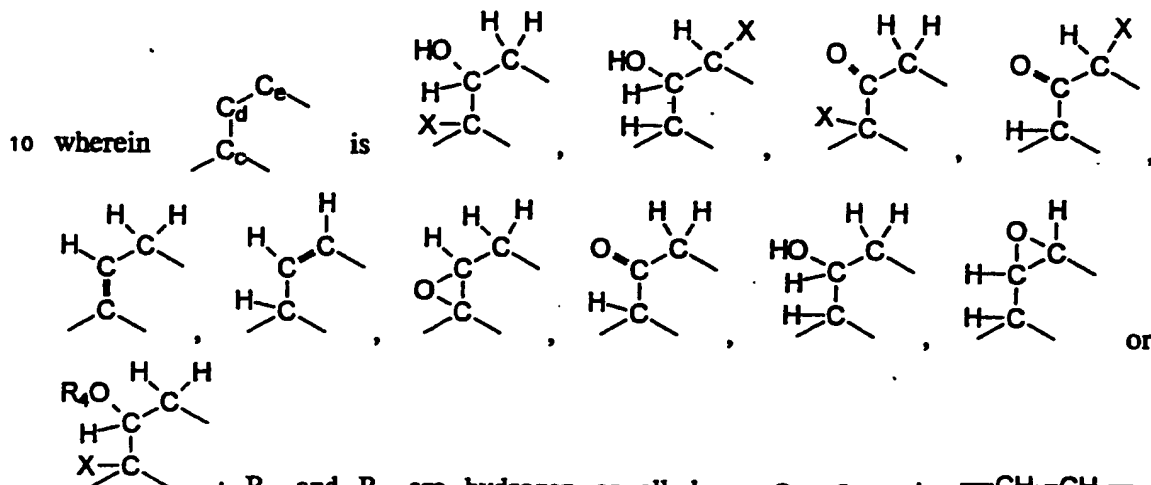
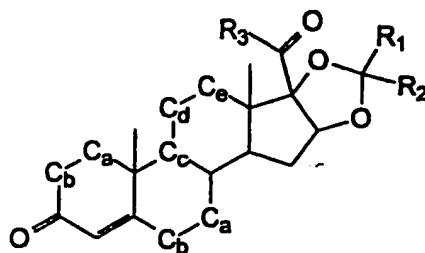
The present inventors have recently demonstrated that intravitreal injection of an anti-inflammatory steroid in depot form substantially arrests and/or reverses AMD and NMD.

It has been shown^{8,9} that intravitreal administration of anti-inflammatory steroids
35 inhibits vascular proliferation in the eye. The inventors have shown^{1,2,3,4,5} in human patients that AMD is promoted by choroidally derived inflammatory cells. The inventors recently described resident immunocompetent cells⁵ in the neural retina which would be subject to the influence of intravitreal anti-inflammatory steroids.

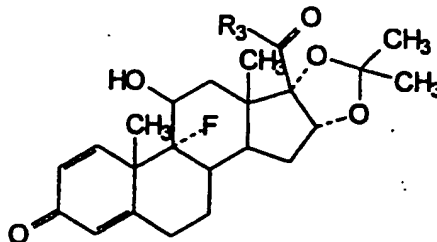
Disclosure Of The Invention

According to a first form of this invention there is provided a method for the treatment or prophylaxis of macular degeneration in a patient requiring said treatment or prophylaxis, comprising administering by intravitreal injection to said patient an effective amount in depot form of an anti-inflammatory steroid which is preferably sparingly soluble in the vitreous.

Preferred steroids include 11-substituted 16 α ,17 α -substituted methylenedioxy steroids of the formula

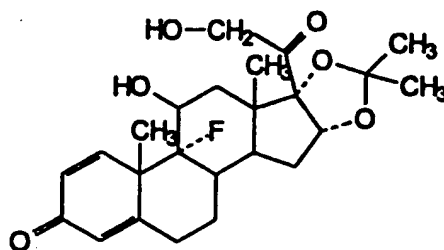


More preferred are compounds of the formula



wherein R₃ is hydroxymethyl, phenylcarbonylaminoisopropylcarbonyloxymethyl, or 2,2-dimethylpropylcarbonyloxymethyl.

The preferred steroid is crystalline 9-fluoro-11,21-dihydroxy-16,17-[1-methylethylidenebis(oxy)]pregna-1,4-diene-3,20-dione:



This compound, also known by its generic name as triamcinolone acetonide is suitably prepared by known methods^{10,11,12,13}.

The steroids are preferably crystalline and are administered in distilled water with a minimum of carriers or adjuvants. However, a depot pharmaceutical composition comprising an effective amount of said anti-inflammatory steroid together with a pharmaceutically and ophthalmologically acceptable carrier, diluent and/or excipient may be used.

When triamcinolone acetonide is used, such a preparation may be made up by using Kenacort-A40 (registered trade mark) (Squibb) as the anti-inflammatory steroid. Suitable pharmaceutically acceptable salts of this compound may be used. For example, the acetate of triamcinolone acetonide may be used.

As the steroids suitable for use in this invention are sparingly soluble in the vitreous, crystalline forms are suitable for administration. The steroids may be formulated with carriers, diluents and/or excipients which are compatible with the vitreous and which do not leave any vision impairing residue in the eye.

The composition of the present invention is administered by intravitreal injection by methods known in the art. For example, the eye is washed with a sterilising agent such as Betadine and the steroid is injected in distilled water with a fine gauge (eg. 27gauge) needle at a position in the eye such that the steroid crystals will settle to the posterior pole towards the ventral surface. It may also be necessary to prepare the eye for injection by application of positive pressure prior to injection. In some cases, paracentesis may be necessary.

The steroid should be as concentrated as feasible to minimise the volume to be injected. The dosage of steroid may be between about 1mg and about 8mg. Typically, 4mg of steroid is deposited intravitreally and thus it is necessary to inject 0.1mL of Kenacort-A40 solution. This dosage range is applicable to each of the three following stages of macular degeneration, namely: early onset macular degeneration, atrophic macular degeneration (AMD) and neovascular macular degeneration (NMD).

The frequency of method of treatment of this invention is not more than 3 monthly. In many cases, a single administration *per annum* may be sufficient.

The compositions of this invention may also be presented as a unit dose in a syringe ready for administration.

The method of the present invention may be practised alone or in conjunction with other therapy. Where laser treatment of the retina is indicated, steroid may be injected before or after the laser treatment. Other substances, for example antibiotics and anti-angiogenesis agents for example thalidomide, may be injected with the steroid.

5 In more than 50% of cases where AMD occurs in one eye, it will occur in the other eye within one year. Prophylactic administration of steroid into an unaffected eye may be useful in such cases.

Brief Description of Drawing

Figure 1 is a comparison between change in visual acuity in three groups of
10 patients.

Best Modes And Other Modes For Carrying Out The Invention

An effective amount of triamcinolone acetonide to arrest and/or reverse macular degeneration is administered by intravitreal injection when such a procedure is indicated.

The present invention will now be described with reference to the following
15 examples which should not be construed as limiting on the scope thereof.

Example 1

Kenacort-A40 (Squibb) (40mg/mL) as supplied is prepared for administration of 0.1mL.

Example 2

20 Six patients were injected with 0.1mL Kenacort-A40. The patients were monitored weekly by direct observation including colour vision, electrophysiological responses of the retina and dynamic studies of the retinal circulation using fluorescein angiography.

Example 3

The influence of intravitreal triamcinolone on microglial distributions in AMD: a
25 case study

The source of the signals which initially provoke choroidal neovascularisation has not been defined, although immune mediation of neovascularisation by both choroidally derived leucocytes and retinal microglia remain significant possibilities. As part of a pilot study, one patient with subfoveal choroidal new vessels received intravitreal triamcinolone
30 in her left eye. Angiography showed that exudation decreased and vision improved. Unfortunately, the patient died within 6 weeks of the administration as a result of cardiovascular failure, but donated her eyes for histopathological examination. The immunohistopathological findings of this unique case study are summarised below.

Methods: Eyes were fixed in 2% paraformaldehyde for 24 hours at 4°C. The delay
35 between death and fixation of both eyes was 25 hours. Following fixation, the neural retina was separated from RPE (ie retinal pigment epithelium)/choroid portion which was postfixed and examined histopathologically in semithin sections. Primary monoclonal

antibodies (MHC class II & CD45) were applied to retinal wholemounts and detected using silver-toned immunogold.

The distributions and phenotypic characteristics of microglia in normal age-matched adult retinac, the treated and untreated retinac were compared.

6 Results: Both the treated and the untreated RPE/choroidal specimens showed similar early disciform lesions which were not obviously altered as a result of the steroid administration. Microglia were morphologically hypertrophic in the untreated retina while the number of microglia was not significantly increased, consistent with our earlier findings. However microglial morphology was less ramified and cell numbers were
10 significantly less in the treated retina.

Conclusions: Comparison of microglial numbers labelled with MHC class II and CD45 antibodies indicated that in addition to reduced cell numbers, triamcinolone administration effected reduced expression of MHC class II by microglia, but not vascular elements.

15

Example 4

Comparison between change in visual acuity in triamcinolone treatment and laser treatment

Figure 1 graphically illustrates a comparison between the change in visual acuity in a group of patients treated with triamcinolone, and a previous study involving a group of
20 patients treated with laser therapy and a group of patients in which no treatment was given (control group). The triamcinolone group was studied for 10 months. The two previously reported groups were studied for a period of 42 months.

The table on the following page sets out the results for the triamcinolone group.

It can be seen from the graph in Figure 1 that there was in fact an initial increase in
25 visual acuity in the triamcinolone group. The group treated with laser therapy suffered a decrease of 3 lines of visual acuity within 3 months. This then remained stable for a period of up to 42 months. The control group experienced less of an initial, decrease falling to 2 lines within 3 months. However, the control group steadily decreased over the period of study, reaching a decrease of 5 lines of visual acuity by 42 months.

Table

Patient No	Age/Sex:	Eye:	Visual Acuity					Disorder (Treated Eye Only)	Drusen
			0/12	1/12	3/12	6/12	10/12		
1.	80/F	Left	1	p5	p5	p5	p5	mCNV + occCNVs + HAEM + hEx + Oed	No
2.	82/M	Left	1	0	0	0	0	ICNV + fib + mHAEM + EBF + Oeb	Few s
3.	80/F	Right	9	p2	m2	m2	m6	sCNV + EBF + Pigdist + Oed	No
4.	78/F	Right	10	p2	0	m0.5	p3	sCNV + EBF + Pigdist + Oed	Few h
5.	84/M	Right	3	p1	p3	p4	p4	mCNV + occCNV + sHAEM + EBF + hEx	No
6.	78/F	Left	8.5	p1	p0.5	m1.5	m1.5	mCNV + Pigdist + EBF + Oed	No
7.	90/F	Left	0.5	0	0	p0.5	N	mCNV + EBF + sHAEM + hEx + Oed	No
8.	76/F	Left	8	m1	N	N	N	2(s+m)CNV + Haem	h+c+s+a
9.	80/F	Left	7	0	N	N	N	mCNV + fibr + serDet	Many h
Change			basis	p.1.1	p0.93	p0.78	p0.75		

Lineage of the visual acuities

1 = 1/60	6 = 6/60	11 = 6/9	s = small (<1DA), m = medium (1-2DA)	h = hard
2 = 2/60	7 = 6/36	12 = 6/7.5	l = large (>2DA) occ = occult,	s = soft
3 = 3/60	8 = 6/24	13 = 6/6	fib = fibrosis, serDet = serous detachment	c = calcified
4 = 4/60	9 = 6/18	14 = 6/5	hEx = hard exudates, EBF = elevated blocked fluorescence	a = atrophic
5 = 5/60	10 = 6/12	15 = 6/4	Pigdist = pigment disturbance	

Industrial Applicability

It should be clear that the methods of treatment of this invention will find wide use in the medical field.

The foregoing describes only some embodiments of the present invention and
5 modifications obvious to those skilled in the art can be made thereto without departing from the scope of the invention.

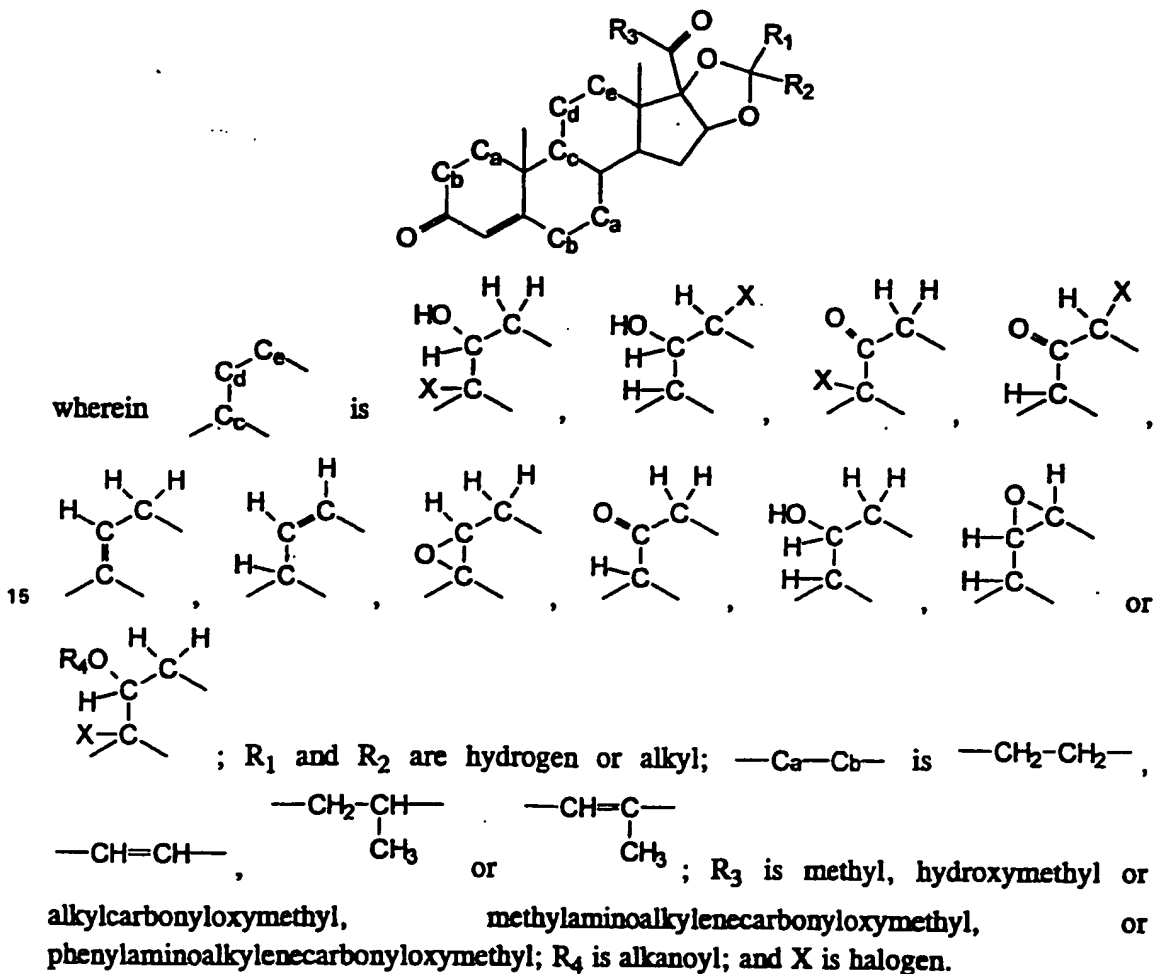
References

- 1 Penfold P L *et al.*, "Senile macular degeneration: The involvement of Immunocompetent cells" Graefe's Arch Clin Exp Ophthalmol (1985) 223:69-76.
- 10 2 Penfold P L *et al.*, "Senile Macular Degeneration The Involvement of Giant Cells in Atrophy of the Retinal Pigment Epithelium" Invest Ophthalmol Vis Sci (1986) 27:364-371.
- 3 Penfold P L *et al.*, "Age-related macular degeneration: ultrastructural studies of the relationship of leucocytes to angiogenesis" Graefe's Arch Clin Exp Ophthalmol (1987)
15 225:70-76.
- 4 Penfold P L *et al.*, "Autoantibodies to retinal astrocytes associated with age-related macular degeneration" Graefe's Arch Clin Exp Ophthalmol (1990) 228:270-274.
- 5 Penfold P L *et al.*, "Antibodies to human leucocyte antigens indicate subpopulations of microglia in human retina" Visual Neuroscience (1991), 7, 383-388.
- 20 6 Dayton L "Treatment for blindness challenges eye orthodoxy" New Scientist 21 March 1992.
- 7 Gehrs K M *et al.* "Transmission Electron Microscopic Study of a Subretinal Choroidal Neovascular Membrane due to Age-Related Macular Degeneration" Arch Ophthalmol (1992) 110, 833.
- 25 8 Ishibashi T *et al.* "Effects of Intravitreal Administration of Steroids on Experimental Subretinal Neovascularization in the Subhuman Primate" Arch Ophthalmol (1985) 103, 708.
- 9 Antoszyk A N *et al.* "The effects of intravitreal triamcinolone acetonide on experimental pre-retinal neovascularization" Graefe's Arch Clin Exp Ophthalmol (1993)
30 231:34-40.
- 10 Fried *et al.*, J. Am. Chem. Soc. 80, 2338 (1958).
- 11 Bernstein *et al.*, *Ibid.* 81, 1689 (1959).
- 12 US 2 990 401.
- 13 US 3 035 050.

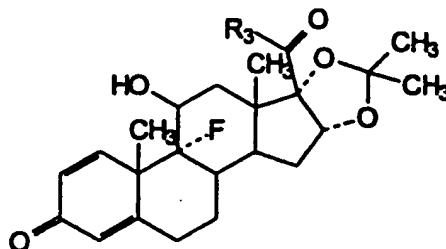
Treatment of Age Related Macular Degeneration

Claims

1. Use of an anti-inflammatory steroid for the manufacture of a medicament for treating macular degeneration by intravitreal injection of said steroid in depot form.
2. Use of an anti-inflammatory steroid by intravitreal injection in depot form for treating macular degeneration.
3. Use according to claim 1 or claim 2, wherein said steroid is in crystalline form.
4. Use according to any one of claims 1 to 3, wherein the steroid is sparingly soluble in the vitreous of the eye.
5. Use according to any one of claims 1 to 4, wherein the steroid is an 11-substituted 16 α , 17 α -substituted methylenedioxy steroid of the formula:

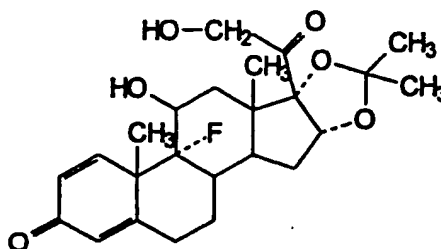


6. Use according to claim 5, wherein the steroid is



wherein R_3 is hydroxymethyl, phenylcarbonylaminoisopropylcarbonyloxymethyl, or 2,2-dimethylpropylcarbonyloxymethyl.

7. Use according to claim 6, wherein the steroid is 9-fluoro-11,21-dihydroxy-16,17-[1-methylethylidenebis(oxy)]pregna-1,4-diene-3,20-dione:



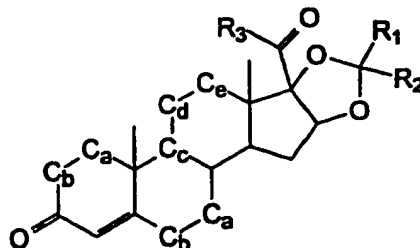
8. Use according to any one of claims 1 to 7, wherein the dosage of steroid is between about 1 and about 8mg.
9. Use according to claim 8, wherein the dosage is about 4mg.
10. Use according to any one of claims 1 to 9, wherein the macular degeneration is early onset macular degeneration, atrophic macular degeneration or neovascular macular degeneration.
11. Use according to any one of claims 1 to 10, of said steroid in conjunction with a further active substance.
12. Use according to claim 11, wherein the further active substance is an anti-angiogenesis agent
13. Use according to claim 12, wherein the anti-angiogenesis agent is thalidomide.
14. Use according to claim 11, wherein the further active substance is an antibiotic.
15. Use according to claim 2, or any one of claims 3 to 14 when dependent on a claim other than claim 1, in conjunction with another therapy.
16. Use according to claim 15, wherein the other therapy is laser treatment of the retina and the anti-inflammatory steroid is injected before or after laser treatment.

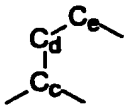
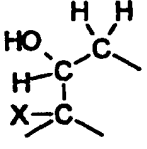
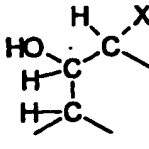
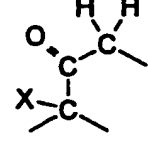
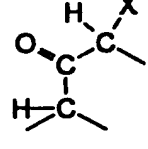
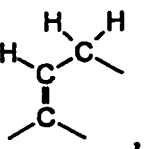
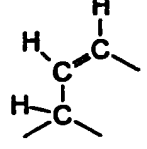
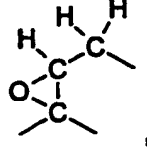
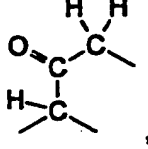
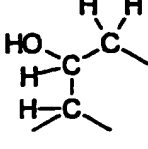
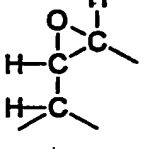
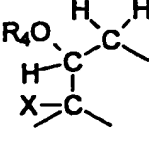
17. A method for the treatment or prophylaxis of macular degeneration in a patient requiring said treatment or prophylaxis, comprising administering by intravitreal injection to said patient an effective amount in depot form of an anti-inflammatory steroid.

18. The method according to claim 17, wherein the steroid is crystalline.

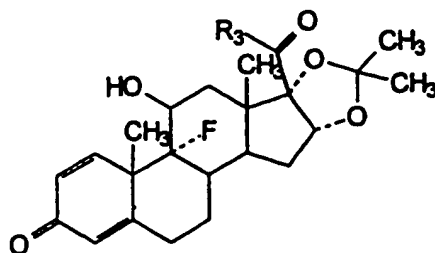
19. The method according to claim 17 or claim 18, wherein the steroid is sparingly soluble in the vitreous of the eye.

20. The method according to any one of claims 17 to 19, wherein the steroid is an 11-substituted 16 α , 17 α -substituted methylenedioxy steroid of the formula



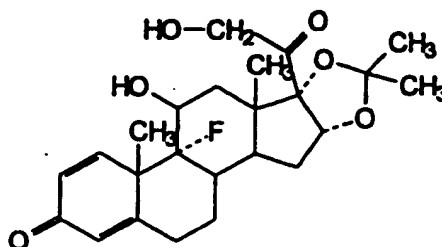
10 wherein  is , , , , , , , , ,  or ; R₁ and R₂ are hydrogen or alkyl; —Ca—Cb— is —CH₂—CH₂—, —CH₂—CH—CH₃, or —CH=CH—CH₃; R₃ is methyl, hydroxymethyl or alkylcarbonyloxymethyl, methylaminoalkylenecarbonyloxymethyl, or phenylaminoalkylenecarbonyloxymethyl; R₄ is alkanoyl; and X is halogen.

21. The method according to claim 20, wherein the steroid is:



wherein R₃ is hydroxymethyl, phenylcarbonylaminoisopropylcarbonyloxymethyl, or 2,2-dimethylpropylcarbonyloxymethyl.

22. The method according to claim 21, wherein the steroid is 9-fluoro-11,21-dihydroxy-16,17-[1-methylethylidenebis(oxy)]pregna-1,4-diene-3,20-dione:



23. The method according to any one of claims 17 to 22 wherein the dosage of steroid is between about 1 and about 8mg.

24. The method according to claim 23 wherein the dosage is about 4mg.

25. The method according to any one of claims 17 to 24 wherein the macular
10 degeneration is early onset macular degeneration, atrophic macular degeneration or neovascular macular degeneration.

26. The method according to any one of claims 17 to 25, comprising a further active substance.

27. The method according to claim 26, wherein the further active substance is an
15 anti-angiogenesis agent.

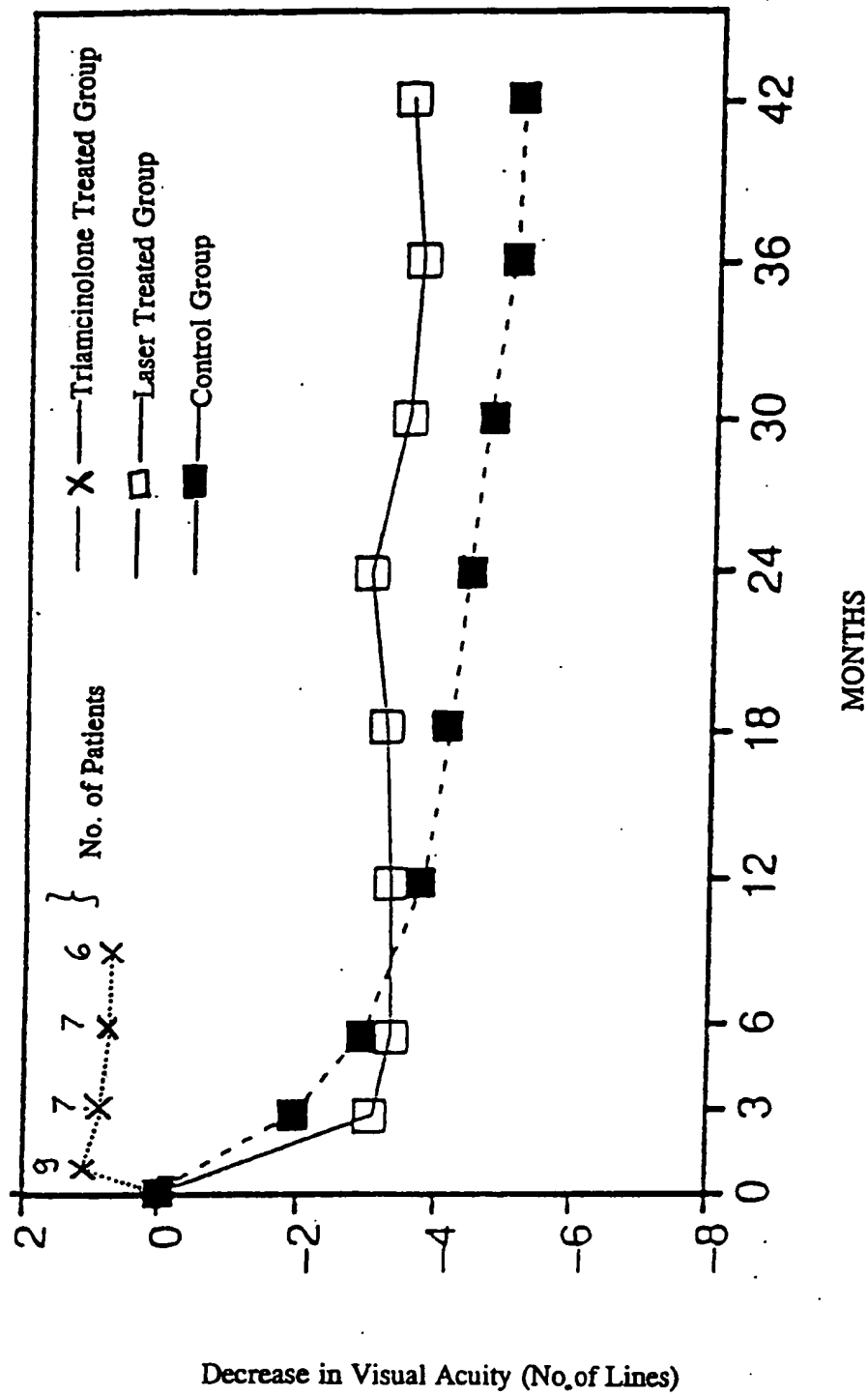
28. The method according to claim 27, wherein the anti-angiogenesis agent is thalidomide.


29. The method according to claim 26, wherein the further active substance is an antibiotic.

20 30. The method according to any one of claims 17 to 29, wherein the method is practised in conjunction with another therapy.

31. The method according to claim 30, wherein the other therapy is laser treatment of the retina and the anti-inflammatory steroid is injected before or after laser treatment.

1/1



A. CLASSIFICATION OF SUBJECT MATTER Int. Cl. ⁵ A61K 31/57 According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K 31/57 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU: IPC as above Electronic data base consulted during the international search (name of data base, and where practicable, search terms used) WPAT, CASM, A61K: TRIAMCINOLONE ACETONIDE				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.		
X	Patent Abstracts of Japan, C-1181, page 52, JP,A,5-331050 (POLA CHEM IND INC) 14 December 1993 (14.12.93)	1-16		
X	AU 16150/83 (SHIONOGI & CO LTD) 5 January 1984 (05.01.84) whole document	1-16		
X	US 3962430 (O'NEILL) 8 June 1976 (08.06.76) whole document, column 7, example 11	1-31		
X	US 3758686 (SIEGER et al) 11 September 1973 (11.09.73) whole document, column 4, example 5	1-31		
<div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. </div> <div> <input checked="" type="checkbox"/> See patent family annex. </div> </div>				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="width: 50%; vertical-align: top;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>			
Date of the actual completion of the international search 6 October 1994 (06.10.94)		Date of mailing of the international search report 8 Nov 1994 (8.11.94)		
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (06) 2853929		Authorized officer  J.P. PULVIRENTI Telephone No. (06) 2832251		

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
X	Antoszyk A.N. et al, Gracfe's Arch Clin Exp Ophthalmol (1993) 231, 34-40	1-31
X	Ishibashi et al, Arch Ophthalmol (1985) 103, 708	1-31

Patent Document Cited in Search Report		Patent Family Member	
AU	16150/83	EP JP	97374 58225009
GB	8317099	GB	2122087
US	3962430	DE	1617628
US	3758686		
JP	5331050		

END OF ANNEX

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.